REMARKS

Claims 1, 2, 4, 5, and 7-11 are currently pending. Claims 7-11 are withdrawn from consideration. Therefore, claims 1, 2, 4, and 5 are presented for further examination on the merits. Applicants thank the Examiner for reviewing the instant application and respectfully request a further review in light of the comments below.

Rejection under 35 U.S.C. § 102(b) – Anticipation

The Examiner rejected Claims 1, 2, 4, and 5 under 35 U.S.C. § 102(b) as anticipated by Kumar et al. (*Synthesis and Evaluation of a New Class of Nifedipine Analogs with T-Type Calcium Channel Blocking Activity*, Mol. Pharmacol. 61:649-658, 2002) ("Kumar"). According to the Examiner, Kumar teaches the elected species by providing the structure represented by PPK 1-16 and particularly PPK-5 for use in blocking T-type calcium channels. The Examiner further argues that Kumar inherently anticipates administering the antagonist "in regular doses no more often than once per day" as recited by independent Claim 1. In the Examiner's view, the limitation "in regular doses no more often than once per day" is an inherent use of any pharmaceutical composition administered by mouth to a patient in need of such treatment. *Office Action* page 4. No recitation of dosing at once per day or less is found or cited in the reference. Therefore, Applicants disagree with this unsupported characterization of the reference's teachings.

The Examiner supports rejection of the claims as inherently anticipated by citing case law holding that claiming a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *Id.* A claim is anticipated only if each and every element of the claim is expressly or inherently found in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987); MPEP § 2131. Moreover, inherency is established only when the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill in the art. Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *See In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) and MPEP § 2112.

Administration "in regular doses no more often than once per day" is a method element that is not inherently present in a pharmaceutical composition or use thereof. This is so because administration of a particular dose at a chosen frequency is neither a necessarily present property of the composition itself nor a necessarily present use. The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. MPEP § 2112 (citing *In re Rijckaert*, 9 F.3d 1531,1534 (Fed. Cir. 1993) (emphasis original). Here, just as the elected species may be chosen to be administered in regular doses more often than once per day, it theoretically may also be chosen to be administered as claimed: in regular doses no more often than once per day. The Examiner appears to take the position that the method element of administering a certain dose under a particular schedule is inherent because "it would be instantly apparent to the one of skill in the pertinent art..." *Office Action* page 4. Whether or not it would be instantly apparent to one of ordinary skill in the art is an obviousness argument that it would be possible or perhaps probable to perform the dose administration step. However, inherency may not be established by probabilities or possibilities. MPEP § 2112. The prior art does not require that a user always and necessarily administer it in regular doses no more often than once per day. Accordingly, Kumar does not inherently anticipate Claim 1.

Furthermore, Kumar does not provide data that mandates the method element of "administering the antagonist to a mammal in regular doses no more often than once per day." The Examiner indicates that Kumar anticipates the claimed invention by teaching a concentration ranging from 0.3 μM -3 μM of PPK-5 on transiently expressed T-type channels in cell lines according to Figure 6, graphs A and B. From these data showing time course block and current block by PPK-5 *in vitro*, no particular dose administration method in a mammal is *necessarily* present or required. More simply, Kumar teaches *in vitro* testing, not the claimed *in vivo* administration to a mammal. Therefore, Kumar does not inherently anticipate administering the antagonist "in regular doses no more often than once per day" as recited by independent Claim 1.

Because Kumar fails to inherently require administering the elected species "to a mammal in regular doses no more often than once per day," Kumar does not meet every element of independent Claim 1. Accordingly, Kumar does not anticipate Claim 1 or Claims 2, 4, and 5 dependent therefrom. Applicants therefore respectfully request the Examiner to reconsider and

withdraw the rejection of Claims 1, 2, 4, and 5 under 35 U.S.C. § 102(b) as anticipated by Kumar.

Rejection under 35 U.S.C. §103(a) – Obviousness

The Examiner rejected Claims 1, 2, 4, and 5 under 35 U.S.C § 103(a) as unpatentable over Kumar in view of Kobrin et al. (*Safety of Mibefradil, a New Once-A-Day, Selective T-Type Calcium Channel Antagonist*, The American Journal of Cardiology, Vol. 80 [48], 1997, printed pages 1-7) ("Kobrin") and U.S. Patent Publication No. 2001/0049447 to Li et al. ("Li"). Applicants respectfully disagree.

It is well settled that the PTO "bears the initial burden of presenting a *prima facie* case of unpatentability..." *In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007). Until the PTO has established a *prima facie* case of obviousness, Applicants need not present arguments or evidence of non-obviousness. To support a *prima facie* case of obviousness, the combination of prior art must teach or suggest all of the elements of a claim. M.P.E.P. § 2141. Further, there must be a "clear articulation of the reason(s) why the claimed invention would have been obvious." M.P.E.P. § 2142. As discussed more fully below, the art cited by the Examiner does not teach all of the elements of independent Claim 1 and the Examiner's articulated reasons why the claimed invention would have been obvious are factually incorrect.

Rejection of Claims 1, 2, 4, and 5 over Kumar in view of Kobrin and Li

According to the Examiner, Kumar teaches the claimed elected species by providing the structure represented by PPK 1-16 and PPK-5 in particular. The Examiner also states that Kumar teaches the use of PPK-5 in the blocking of T-Type Calcium Channels. Moreover, the Examiner concludes that Kumar teaches that the elected species and nifedipine have the same mechanism of action, same affinity toward the same receptors, and similar activity. *Office Action* pages 6-8.

The Examiner notes that Kumar does not teach "prodrug" or "once a day dosing of a T-Type channel antagonist," but asserts Li and Kobrin provide these missing elements, respectively, with regard to nifedipine. The Examiner also characterizes nifedipine as a T-type calcium channel blocker just like the elected species. *Office Action* page 7. Based on the foregoing premise, i.e., that both the elected species and nifedipine are selective T-type blockers

with similar properties, the Examiner concludes that one of ordinary skill would combine the teachings of these references with a reasonable expectation of success. As such, the Examiner concludes that Kumar, Kobrin, and Li establish a *prima facie* case of obviousness. Applicants disagree.

Contrary to the Examiner's contention, the elected species of Claim 1 does not have the same mechanism of action, affinity toward the same receptors, or activity as nifedipine. This is because the elected species is a selective T-type calcium channel blocker and nifedipine is not. Rather, nifedipine is in fact a selective L-type calcium channel blocker. Although the Examiner in the Office Action characterizes nifedipine as a T-Type blocker, Kumar demonstrates otherwise. Figure 6D of Kumar is a bar graph in log scale comparing the relative selectivities of nifedipine and PPK-5 toward L-type (α_{1c}) and T-type (α_{1G}) Calcium Channels in terms of IC_{50} values. Interpreting the data, Kumar discloses, "Whereas nifedipine blocked L-type channels more effectively than T-type channels by almost 3 orders of magnitude...PPK-5 exhibited a 40-fold selectivity for T-type over L-type channels." *See* Kumar, page 654, 2nd column (emphasis added). Referring to the side-by-side comparison between nifedipine and PPK-5, Kumar concludes, "Thus, L-type and T-type calcium channels require distinct drug structural requirements for effective DHP block." *Id.*

Because nifedipine is not a T-type calcium channel blocker, but rather a selective L-type blocker, the data in Kumar are consistent in showing that the elected species and nifedipine actually have a markedly different mechanism of action and activity. The Examiner directed attention to Kumar at page 654, col. 2 to page 655, col. 1, 1st paragraph as teaching similarity of mechanism of action between the claimed compound and nifedipine. The cited passages, however, show the opposite: nifedipine does not block current activity of T-type calcium channels. By contrast, PPK-5 does block T-type calcium channel current activity and is merely antagonized by nifedipine, which increases the PPK-5 time constant approximately twofold.

Far from meaning that the claimed compound and nifedipine have similar mechanism of action or activity, as the Discussion section of Kumar explains, "Thus, we conclude that nifedipine is able to bind to a DHP interaction site on the T-type calcium channel molecule without significantly inhibiting current flux." *See* Kumar at page 656, 2nd column (emphasis added). Kumar continues to explain, "[W]e favor a model in which the two compounds compete

for the same site, but because of its bulkier substituents, PPK-5 is able to effectively block channel activity whereas nifedipine is not." *Id.* (emphasis added) Although PPK-5 and nifedipine may have an overlapping binding site on T-type calcium channels, Kumar is unambiguous with regard to the fact that PPK-5 has blocking activity whereas nifedipine does not. As such, the claimed compound and nifedipine do not have the same mechanism of action or activity. Notably, the cited passage from the Methods section in Kumar, which the Examiner views as showing that the claimed compound and nifedipine have the same affinity toward the same receptors, does not even discuss either compound's affinity at all. *See* Kumar, Methods, 2nd col., 1st paragraph (describing synthesis schemes).

In order to establish a *prima facie* case of obviousness, the combination of prior art must teach or suggest all of the elements of a claim. M.P.E.P. § 2142. For the reasons explained above, combining the disclosures of Kumar, Kobrin, and Li with regard to nifedipine fails to teach or suggest a method for inhibiting calcium T-channel activity comprising the steps of providing a selective T-channel antagonist, as recited in Claim 1. The combined cited references with regard to nifedipine do not teach or suggest a selective T-channel antagonist, much less one having an onset of activity in reducing blood pressure *in vivo* and a duration of activity *in vivo*, as provided in Claim 1. Indeed, Kumar does not teach any *in vivo* activity of the compounds studied, let alone a time course of *in vivo* activity. Rather, Kumar only discloses *in vitro* data.

Kobrin and Li do not teach or suggest the elements missing from Kumar; including a method for inhibiting calcium T-channel activity comprising the steps of providing a selective T-channel antagonist and administering the selective T-channel antagonist to a mammal in regular doses no more often than once per day. As the combination of Kumar, Kobrin, and Li fail to teach or suggest all elements of Claim 1, Applicants respectfully request the Examiner's rejection of Claim 1 and all claims dependent therefrom be withdrawn.

To support a *prima facie* case of obviousness, there must also be a "clear articulation of the reason(s) why the claimed invention would have been obvious." M.P.E.P. § 2142. Here, such requisite articulation is insufficient because the key factual assertion on which the rejection was based is false: nifedipine is not a selective T-type calcium channel blocker. A person of ordinary skill would not have reason to combine the teachings of a selective L-channel antagonist to perform the method of Claim 1, which comprises providing a selective T-channel antagonist

having markedly dissimilar mechanism of action and activity according to Kumar. Furthermore, there is no reasonable expectation of success where the combination of references fails to teach or suggest providing a selective T-channel antagonist, but instead teaches a compound that is selective for a different type of calcium channel and indeed has almost no effect on T-channel current activity. Applicants respectfully request the Examiner's rejection of Claim 1 and all claims dependent therefrom be withdrawn because the combination of references cited in the Office Action fails to establish a *prima facie* case of obviousness.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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